**Medical Policy**

**MP 5.01.10**  
Immune Prophylaxis for Respiratory Syncytial Virus

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**BCBSA Ref. Policy:** 5.01.10  
**Related Policies:** None  
**Last Review:** 08/20/2018  
**Effective Date:** 08/20/2018  
**Section:** Prescription Drugs

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**DISCLAIMER**

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

**POLICY**

Monthly administration of immune prophylaxis for respiratory syncytial virus (RSV) with palivizumab during the RSV season may be considered **medically necessary** in the following infants and children in accordance with guidelines-based recommendations (American Academy of Pediatrics [2014]):

1. In the first year of life, ie, younger than 12 months at the start of the RSV season or born during the RSV season:
   a. Infants born before 29 weeks, 0 days of gestation;
   b. Preterm infants with chronic lung disease (CLD) of prematurity, defined as birth at less than 32 weeks, 0 days of gestation and a requirement for more than 21% oxygen for at least the first 28 days after birth;
   c. Certain infants with hemodynamically significant heart disease (eg, infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures; infants with moderate-to-severe pulmonary hypertension; infants with lesions adequately corrected by surgery who continue to require medication for heart failure);
      i. Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist.
   d. Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways (eg, ineffective cough, recurrent gastroesophageal tract reflux, pulmonary malformations, tracheoesophageal fistula, upper airway conditions, or conditions requiring tracheostomy);
   e. Children with cystic fibrosis who have at least one of the following conditions:
      i. Clinical evidence of CLD; and/or
      ii. Nutritional compromise.

2. In the second year of life, ie, younger than 24 months at the start of the RSV season:
   a. Children who were born at less than 32 weeks, 0 days of gestation and required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroid, or diuretic therapy) during the 6-month
period before the start of the second RSV season.
b. Children with cystic fibrosis who have either:
   i. Manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persists when stable); or
   ii. Weight for length less than the 10th percentile.
3. In the first or second year of life:
a. Children who will be profoundly immunocompromised (eg, will undergo solid organ or hematopoietic cell transplantation or receive chemotherapy) during the RSV season.
4. After surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab may be considered medically necessary after cardiac bypass or at the conclusion of extracorporeal membrane oxygenation for infants and children younger than 24 months.

Immunoprophylaxis for respiratory syncytial virus is considered not medically necessary in:

1. Infants and children with hemodynamically insignificant heart disease (eg, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus);
2. Infants with lesions adequately corrected by surgery, unless they continue to require medication for heart failure;
3. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition; or

Other indications for immune prophylaxis for RSV are considered investigational including, but not limited to, controlling outbreaks of health care–associated disease; or use in children with cystic fibrosis or Down syndrome without other risk factors; or in children over 2 years of age, unless criteria for medical necessity (outlined above) are satisfied.

**POLICY GUIDELINES**

**DOSING AND ADMINISTRATION**

Palivizumab is administered by intramuscular injection at a dose of 15 mg/kg of body weight per month. The anterolateral aspect of the thigh is the preferred injection site. Routine use of the gluteal muscle for the injection site can cause sciatic nerve damage.

Clinicians may administer up to a maximum of 5 monthly doses of palivizumab (15 mg/kg per dose) during the respiratory syncytial virus (RSV) season to infants who qualify for prophylaxis. Qualifying infants born during the RSV season will require fewer doses. For example, infants born in January would receive their last dose in March (see Initiation and Termination of Immunoprophylaxis subsection below) (American Academy of Pediatrics [2014]).

Hospitalized infants who qualify for prophylaxis during the RSV season should receive the first dose of palivizumab 48 to 72 hours before discharge or promptly after discharge.

**Breakthrough RSV**

Guidelines make the following recommendation on breakthrough RSV: “If any infant or young child receiving monthly palivizumab prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood (<0.5%) of a second RSV hospitalization in the same season” (AAP [2014]).
PREVENTION OF HEALTH CARE‒ASSOCIATED RSV DISEASE
RSV is known to be transmitted in the hospital setting and to cause serious disease in high-risk infants. Among hospitalized infants, the most effective ways of reducing RSV transmission is to strictly observe common infection control practices; this includes the restriction of visitors to the neonatal intensive care unit during peak respiratory virus season, and to promptly initiate all standard precautions when coming into contact with RSV-infected infants. If an RSV outbreak occurs in a high-risk unit (eg, pediatric or neonatal intensive care unit or stem cell transplantation unit), primary emphasis should be placed on proper infection control practices, especially hand hygiene. No data exist to support palivizumab use for controlling outbreaks of health care‒associated disease, and the use of palivizumab is not recommended for this purpose.

INTERACTIONS
Palivizumab does not interfere with response to other scheduled childhood vaccines. However, palivizumab may interfere with RSV diagnostic tests that are immunologically based (eg, some antigen detection-based assays).

RISK MINIMIZATION TECHNIQUES
For all infants, particularly those who are preterm, the environment should be optimized to prevent RSV and other viral respiratory infections by doing the following: offering breast milk feeds, immunizing household contacts with influenza vaccine, practicing hand and cough hygiene, by avoiding tobacco or other smoke exposure, and by not attending large group child care during the first winter season, whenever possible (Technical report: updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. Aug 2014;134(2):e620-e638. PMID 25070304).

INITIATION AND TERMINATION OF IMMUNOPROPHYLAXIS
Initiation of immunoprophylaxis in November and continuation for a total of 5 monthly doses will provide protection into April and is recommended for most areas of the United States. If prophylaxis is initiated in October, the fifth and final dose should be administered in February.

In the temperate climates of North America, peak RSV activity typically occurs between November and March, whereas in equatorial countries, RSV seasonality patterns vary and may occur throughout the year. The annual occurrence of the RSV season is predictable, but the severity, time of onset, peak activity, and end of the season cannot be predicted precisely. Substantial variation in timing of community outbreaks of RSV disease from year to year exists in the same community and between communities in the same year, even in the same region. These variations occur within the overall pattern of RSV outbreaks, usually beginning in November or December, peaking in January or February, and ending by late March or sometime in April. Communities in the southern United States, particularly in Florida, tend to experience the earliest onset of RSV activity. In recent years, the national duration of the RSV season has been 21 weeks (MMWR [2013]).

Clinical trial results have indicated that palivizumab trough serum concentrations more than 30 days after the fifth dose will be well above the protective concentration for most infants. Five monthly doses of palivizumab will provide more than 20 weeks of protective serum antibody concentration. In the continental United States, a total of 5 monthly doses for infants and young children with congenital heart disease, chronic lung disease of prematurity, or preterm birth before 32 weeks of gestation (31 weeks, 6 days) will provide an optimal balance of benefit and cost, even with variation in season onset and end.
Data from the Centers for Disease Control and Prevention have identified variations in the onset and offset of the RSV season in Florida that affect the timing of palivizumab administration. Northwest Florida has an onset in mid-November, which is consistent with other areas of the United States. In North Central and Southwest Florida, the onset of RSV season typically is late September to early October. The RSV season in Southeast Florida (Miami-Dade County) typically has its onset in July. Despite varied onsets, the RSV season is of equal duration in the different regions of Florida. Children who receive palivizumab prophylaxis for the entire RSV season should receive palivizumab only during the 5 months after the onset of RSV season specific to their region (maximum of 5 doses).

**BENEFIT APPLICATION**

**BLUE CARD/NATIONAL ACCOUNT ISSUES**
State or national mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration‒approved biologics may not be considered investigational, and thus, these biologics may only be assessed on the basis of their medical necessity.

**BACKGROUND**

**RESPIRATORY SYNCYTIAL VIRUS INFECTIONS**
Respiratory syncytial virus (RSV) infections typically occur in the winter months, starting from late October to mid-January and ending anywhere from March to May. Considerable variation in the timing of community outbreaks is observed from year to year. According to U.S. Centers for Disease Control and Prevention, the onset of the RSV season occurs when the median percentage of specimens testing positive for RSV is 10% higher over a 2-week period. Annually in the United States, RSV infection has been associated with an estimated 57,527 hospitalizations and 2.1 million outpatient visits among children less than 5 years of age. While RSV is a near-ubiquitous infection, infants with underlying medical issues, especially a history of prematurity with associated lung problems, are at risk of developing serious complications from bronchiolitis secondary to RSV.

**CHRONIC LUNG DISEASE**
Chronic lung disease (CLD) of prematurity (formerly known as bronchopulmonary dysplasia) is a general term for long-term respiratory problems in premature infants. CLD results from lung injury to newborns who consequently must use a mechanical ventilator and supplemental oxygen for breathing. With injury, lung tissues become inflamed, and scarring can result. Causes of lung injury include the following: prematurity, low amounts of surfactant, oxygen use, and mechanical ventilation. Risk factors for developing CLD include birth at less than 34 weeks of gestation; birth weight less than 2000 grams (4 pounds, 6.5 ounces); hyaline membrane disease; pulmonary interstitial emphysema; patent ductus arteriosus; Caucasian race; male sex; maternal womb infection (chorioamnionitis); and family history of asthma.

**Treatment**
Palivizumab (Synagis) is a humanized monoclonal antibody, made using recombinant DNA technology, directed against a site on the antigenic site of the F protein of RSV. Other RSV preventive agents, including vaccines, have been under development. A recombinant RSV fusion protein nanoparticle vaccine has been shown to induce an immune response in a phase 2 trial. This evidence review does not address therapies to treat RSV infection.
REGULATORY STATUS
In 1998, the biologic drug palivizumab (Synagis®; MedImmune) was approved for marketing by the Food and Drug Administration through a biologics license application (103770) for use in the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease. In 2004, the Food and Drug Administration approved a liquid formulation of Synagis®, supplied as a sterile solution ready for injection, thus providing improved convenience for administration. This formulation is used in the physician office or home setting. There are no therapeutic equivalents to this drug.

RATIONALE
This evidence review was created in March 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 4, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

IMMUNE PROPHYLAXIS FOR RESPIRATORY SYNCYTIAL VIRUS

Clinical Context and Therapy Purpose
The purpose of immune prophylaxis for respiratory syncytial virus (RSV) in patients at increased risk for RSV in infancy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of immune prophylaxis for RSV improve the net health outcome in infants with various conditions increasing their risk for RSV?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest in this review include:

- Infants at high risk for RSV (eg, prematurity, coronary heart disease, or chronic lung disease)
- Infants with cystic fibrosis without other risk factors for RSV
- Infants with immunodeficiencies without other risk factors for RSV
- Infants with Down syndrome without other risk factors for RSV.
**Interventions**
The therapy being considered is immune prophylaxis for RSV. Currently, palivizumab (Synagis) is approved by the Food and Drug Administration for this indication. Treatment is administered once monthly for a maximum of 5 doses, during RSV season. In the United States, RSV season occurs typically from November to March. Monthly prophylaxis should be discontinued if an RSV infection or hospitalization occurs.

**Comparator**
The comparator is routine care without immune prophylaxis.

**Outcomes**
The general outcome of interest is the RSV hospitalization rate. Other outcomes include RSV infection rates and adverse events.

**Timing**
Follow-up spans the RSV season, typically 5 months from November through March.

**Setting**
Immune prophylaxis for RSV is administered in a clinician's office.

**High-Risk Infants**

**Systematic Reviews**
A Cochrane review by Andabaka et al (2013) evaluated 3 pivotal RCTs (total N=2831 patients) assessing the efficacy of palivizumab in preventing severe RSV infection in high-risk infants. The review reported a reduction in hospitalization rate from 101 to 50 per 1000 (relative risk, 0.49; 95% confidence interval [CI], 0.37 to 0.64).

Homaira et al (2014) reported on results of a systematic review that included real-world postlicensure studies of RSV prophylaxis. Reviewers included 20 observational studies that generally supported the benefit of RSV in high-risk infants.

**Randomized Controlled Trials**
Several RCTs have demonstrated the success of immune prophylaxis of RSV. Among them, Blanken et al (2013) reported on the findings of the multicenter, double-blind, randomized, placebo-controlled MAKI trial that allocated 429 otherwise healthy preterm infants born at a gestational age of 33 to 35 weeks to monthly palivizumab (n=214) or placebo (n=215) during RSV season. This trial was not included in the 2013 Cochrane review described above. The prespecified primary outcome was the total number of parent-reported wheezing days in the first year of life. Premature infants treated with palivizumab had a significant 61% (95% CI, 56% to 65%) relative decrease in the total number of wheezing days during the first year of life. Moreover, the effect of RSV prevention on the number of wheezing days persisted in the postprophylaxis period (ie, starting at 2 months after the last injection), for a relative reduction of 73% (95% CI, 66% to 80%). Additionally, palivizumab treatment reduced hospitalizations related to RSV infection (12.6% in the RSV prevention group vs 21.9% in the placebo group; p=0.04).

The IMpact-RSV Study (1998) reported on the results of a double-blind RCT that randomized 1502 premature children (≤35 weeks) or children with bronchopulmonary dysplasia during the 1996 to 1997 RSV season to palivizumab or placebo. The primary end point was hospitalization with confirmed RSV infection. Palivizumab resulted in a 55% reduction in RSV hospital admission (4.8% [48/1002] in the
palivizumab group vs 10.6% [53/500] in the no prophylaxis group). Similar reductions in other measures of RSV severity in breakthrough infections also were reported.

Feltes et al (2003) reported on the results of a double-blind RCT that randomized 1287 children with hemodynamically significant congenital heart disease. They receiving palivizumab had a 45% relative reduction in hospitalizations for RSV. Hospitalizations for RSV occurred in 5.3% (34/639) of the palivizumab group and in 9.7% (63/648) of the no prophylaxis group.

Tavou et al (2014) reported on a small RCT that evaluated developmental and growth outcomes for infants born at less than 32 weeks of gestation treated with palivizumab prophylaxis. The trial randomized 83 infants with an indication for palivizumab prophylaxis but without chronic lung disease (infants born at 28 weeks of gestation who were <12 months old and those born at 29-32 weeks of gestation who were <6 months old at the beginning of RSV season) to palivizumab prophylaxis (n=41) or no therapy (control; n=42) over 2 RSV seasons. Subjects in the palivizumab group had significantly lower rates of RSV-related lower respiratory tract infection and hospitalizations than the control group during the first year of prophylaxis (infection, 23.1% vs 53.7%, p=0.005; hospitalizations, 0% vs 24.4%; p=0.001, respectively), with similar differences in the second year of prophylaxis. However, anthropometric indices and results on the Guide for Monitoring Child Development (a developmental assessment tool) at 18 months corrected for age did not differ significantly between groups.

Nonrandomized Studies
Multiple nonrandomized studies have assessed the efficacy of palivizumab in preventing severe RSV infection in high-risk infants. For example, Farber et al (2016) published results of a claims analysis that revealed healthy preterm infants (born at 29 to 36 weeks of gestation treated with at least 1 dose of palivizumab during their first RSV season occurring in 2012, 2013, or 2014) had only a minor absolute difference in RSV hospitalization rates (3.1%) compared with the infants not treated with palivizumab (5.0%; p=0.04). However, the small absolute reduction in the rate of RSV-related hospitalizations favoring palivizumab was offset by increased hospitalizations for bronchiolitis without RSV diagnosis (3.3% vs 1.9%, p=0.05).

Cohen et al (2008) reported a cumulative incidence of RSV hospitalization of 1.9% among patients with congenital heart disease who received prophylaxis. Ozyurt et al (2015) reported on the results of a case-control study, although the methods used were more consistent with a retrospective cohort study, that showed lower respiratory tract infections–related hospitalizations were less frequent in the palivizumab prophylaxis group (relative risk, 0.75; p<0.001) compared with those who did not receive palivizumab prophylaxis.

Section Summary: High-Risk Infants
Several RCTs have demonstrated the effectiveness of palivizumab prophylaxis in reducing the risk of RSV-related infection and hospitalizations in infants at high risk for RSV-related infection due to prematurity, chronic lung disease, and congenital heart disease.

Cystic Fibrosis

Systematic Reviews
Robinson et al published a Cochrane review (originally published in 2010 and updated in 2013, 2014 and 2016), which assessed the use of palivizumab in children with cystic fibrosis (CF) based on a literature search through May 2016. Reviewers identified a single RCT that randomized 186 infants (<2 years old) with CF to palivizumab (n=92) or placebo (n=94). One member of each group was hospitalized for RSV within the 6-month follow-up. The incidence of adverse events was relatively high in both groups,
with serious adverse events not differing significantly between the palivizumab (20.2%) and placebo (17.3%) groups. Robinson et al noted that it was not possible to draw conclusions on the safety and tolerability of RSV immune prophylaxis in CF: Although the trial reported similar incidences of adverse events, it did not specify how adverse events were classified, and no clinically meaningful outcome differences were noted at 6-month follow-up. Reviewers called for additional randomized studies to establish safety and efficacy of immune prophylaxis in children with CF.

Sánchez-Solis et al (2015) published a meta-analysis of palivizumab prophylaxis for RSV infection in CF patients. Literature was searched through November 2012; 4 prospective and retrospective observational studies, a questionnaire, and the randomized trial included in the 2014 Cochrane review (described earlier) were selected (total N=617 patients). Historical controls and nonprophylaxed cohorts from 3 other studies were also included. In separate random-effects meta-analyses, weighted mean hospitalization rates were 0.018 (95% CI, 0.007 to 0.048) for 354 palivizumab-treated patients and 0.126 (95% CI, 0.086 to 0.182) for 463 controls, a statistically significant difference (p<0.001). However, in a meta-analysis of the 3 studies that included treated and untreated patients (ie, contemporaneous controls), the between-group difference was not statistically significant (weighted mean hospitalization rate, 0.024 [95% CI, 0.005 to 0.098] for palivizumab-treated patients vs 0.093 [95% CI, 0.037 to 0.218] for controls; p=0.115).

Registry Studies
Groves et al (2016) reported on a retrospective review of a CF registry of 92 children treated from 1997 to 2007, comparing outcomes of those treated before and after palivizumab prophylaxis became routine in 2002. In addition to the study’s primary objective (RSV-related hospitalization rates in pre- and post-2002 cohorts), the authors reported on lung function, growth parameters, and bacterial colonization in both cohorts at age 6. Forty-five patients were born after 2002, and all received palivizumab in their first year of life before RSV season. The overall rate of RSV-related hospitalizations was 13%. The risk of RSV infection among palivizumab nonrecipients was approximately 5 times that for palivizumab recipients (relative risk, 4.78; 95% CI, 1.1 to 20.7).

Section Summary: Cystic Fibrosis
Some evidence, summarized in systematic reviews, has demonstrated reductions in hospitalization rates in palivizumab-treated patients with CF when historical controls were involved in the analysis. However, analyses limited to studies that used contemporaneous controls have not demonstrated reductions in hospitalization rates. In the single RCT, event rates were low and did not differ statistically between palivizumab and placebo. Rates of adverse events were high in both groups, making it difficult to draw conclusions about the net benefit of palivizumab. A more recent nonrandomized study using noncontemporaneous controls found the reduced likelihood of RSV infections in palivizumab-treated compared with palivizumab-untreated patients. Additional studies are needed to establish the benefit of palivizumab in patients with CF.

Immunodeficiencies
The use of palivizumab in children with primary immunodeficiency has not been formally evaluated in clinical trials or in nonrandomized comparative studies. Lanari et al (2014) published a literature review on RSV infection in infants with primary immunodeficiency disorders and speculated that the absence of RCTs assessing palivizumab prophylaxis in immunocompromised infants was attributable to “the low incidence of these disorders and the ethical controversies surrounding them.” In the absence of empirical data to support the use of palivizumab prophylaxis in immunocompromised infants, reviewers cited findings of a consensus panel of pediatric pulmonologists, as reported by Gaboli et al (2014), who
would consider off-label use of palivizumab in primary immunodeficiencies. This recommendation was based on a case report by Manzoni et al (2007) who discussed 2 infants with primary immunodeficiencies and 2 infants with acquired immunodeficiencies in whom palivizumab was used with good compliance and efficacy.

**Section Summary: Immune Deficiencies**

A relatively small body of literature has evaluated the use of palivizumab for RSV immunoprophylaxis in patients with primary or acquired immunodeficiency. Comparative evidence of efficacy is lacking.

**Down Syndrome**

Yi et al (2014) reported on a prospective cohort study that compared RSV infection and related hospitalization in a cohort of children younger than 2 years of age with Down syndrome who received palivizumab during the RSV season between 2005 and 2012 (n=532) with a previously published, similarly untreated Down syndrome birth cohort (n=233). Overall 31 (9.9%) children were hospitalized for RSV (23 untreated, 8 treated). The adjusted risk of RSV-related hospitalizations was higher in untreated subjects than in palivizumab recipients (incidence rate ratio, 3.63; 95% CI, 1.52 to 8.67). The adjusted risk of hospitalization for all respiratory tract infection (147 events; 73 untreated vs 74 treated) was similar (incidence rate ratio untreated vs palivizumab, 1.11; 95% CI, 0.80 to 1.55). Use of a noncontemporaneous control from another country introduced potential bias due to different indications for hospitalization and different environmental factors that could have affected the severity of RSV infection. Therefore, these study design limitations preclude interpretation of the study results.

**Section Summary: Down Syndrome**

One prospective cohort study, which used nonconcurrent controls, has reported reductions in RSV-related hospitalization risk in palivizumab-treated patients with Down syndrome. However, study methodology limited the conclusions that could be drawn from it.

**SUMMARY OF EVIDENCE**

For individuals with high-risk indications for RSV in infancy who receive immune prophylaxis for RSV, the evidence includes several RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and hospitalizations. Evidence from systematic reviews of RCTs has demonstrated that RSV prophylaxis with palivizumab is associated with reductions in RSV-related hospitalizations and length of intensive care unit stays. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with CF without other risk factors for RSV in infancy who receive immune prophylaxis for RSV, the evidence includes an RCT, several prospective and retrospective cohort studies, and multiple systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and hospitalizations. Although some studies have demonstrated reductions in hospitalizations in palivizumab-treated patients, studies that used contemporaneous controls did not. In the available RCT, rates of adverse events were high in both the palivizumab and the placebo groups, making it difficult to draw conclusions about the net benefit of palivizumab. A more recent nonrandomized study using noncontemporaneous controls found fewer RSV infections in palivizumab-treated patients with CF. Additional studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with immunodeficiencies without other risk factors for RSV in infancy who receive immune prophylaxis for RSV, the evidence includes case series. Relevant outcomes are overall survival, symptoms, morbid events, and hospitalizations. Descriptive findings from a consensus panel and case
reports of 2 infants with primary immunodeficiencies and 2 infants with acquired immunodeficiencies in whom palivizumab was used with good compliance and efficacy have been reported in the literature. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with Down syndrome without other risk factors for RSV in infancy who receive immune prophylaxis for RSV, the evidence includes a prospective cohort study. Relevant outcomes are overall survival, symptoms, morbid events, and hospitalizations. The available cohort study reported reduced rates of RSV-related hospitalization in treated patients but had methodologic limitations, including the use of a noncontemporaneous comparative cohort from a different country; such limitations introduce uncertainty into any conclusions that can be made. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 3 physician specialty societies (7 responders) while this policy was under review in 2009. Most providing input agreed with the policy statements; these statements concurred with the 2009 American Academy of Pediatrics guidelines.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Pediatrics

The American Academy of Pediatrics (AAP; 2014) updated its guidelines on the use of palivizumab in high-risk infants. In 2017, the guidelines were reviewed by AAP, the American Academy of Family Physicians, American College of Chest Physicians, American College of Emergency Physicians, and the Committee on Infectious Diseases. Following that review, AAP concluded that its recommendations should remain unchanged (see Table 1).

Table 1. Guidelines on Use of Palivizumab Prophylaxis for Infants

<table>
<thead>
<tr>
<th>Recommendations for Using Palivizumab Prophylaxis</th>
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<tbody>
<tr>
<td><strong>Prophylaxis recommended</strong></td>
</tr>
<tr>
<td>• Infants born before 29 weeks, 0 days of gestation, during first year of life</td>
</tr>
<tr>
<td>• Infants born before 32 weeks, 0 days of gestation with chronic lung disease of prematurity, during first year of life</td>
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<tr>
<td>• Children in the second year of life who require 28 or more days of supplemental oxygen and continue to require medical intervention during respiratory syncytial virus season</td>
</tr>
<tr>
<td><strong>Prophylaxis may be considered</strong></td>
</tr>
<tr>
<td>• Infants with hemodynamically significant heart failure, during first year of life</td>
</tr>
<tr>
<td>• Infants with a pulmonary abnormality or neuromuscular disease that impairs ability to clear secretions from lower airways, during first year of life</td>
</tr>
<tr>
<td>• Children younger than 24 months who are profoundly immunocompromised during respiratory syncytial virus season</td>
</tr>
<tr>
<td><strong>Prophylaxis not recommended</strong></td>
</tr>
<tr>
<td>• Healthy infants born at or after 29 weeks, 0 days of gestation</td>
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</tbody>
</table>
• There is insufficient evidence for children with cystic fibrosis or Down syndrome without other risk factors

AAP (2014) also published guidelines on the diagnosis, management, and prevention of bronchiolitis (updating 2006 guidelines), and made the following recommendations about the use of palivizumab for RSV prevention (see Table 2).²⁸

Table 2. Guidelines on the Diagnosis, Management, and Prevention of Bronchiolitis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>QOE</th>
<th>SOR</th>
</tr>
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<tbody>
<tr>
<td>“Clinicians should not administer palivizumab to otherwise healthy infants with a gestational age of 29 weeks, 0 days or greater.”</td>
<td>B</td>
<td>Strong</td>
</tr>
<tr>
<td>“Clinicians should administer palivizumab during the first year of life to infants with hemodynamically significant heart disease or chronic lung disease of prematurity defined as preterm infants &lt;32 weeks 0 days’ gestation who require &gt;21% oxygen for at least the first 28 days of life.”</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>“Clinicians should administer a maximum 5 monthly doses (15 mg/kg/dose) of palivizumab during the respiratory syncytial virus season to infants who qualify for palivizumab in the first year of life.”</td>
<td>B</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

QOE: quality of evidence; SOR: strength of recommendation.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov in July 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>90378</td>
<td>Respiratory syncytial virus, monoclonal antibody, recombinant, for intramuscular use, 50 mg, each</td>
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<td></td>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
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<td>I35.0-I35.9</td>
<td>Nonrheumatic aortic valve disorders code range</td>
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<tr>
<td></td>
<td>I36.0-I36.9</td>
<td>Nonrheumatic tricuspid valve disorders code range</td>
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<tr>
<td></td>
<td>I37.0-I37.9</td>
<td>Nonrheumatic pulmonary valve disorders code range</td>
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<td></td>
<td>I42.0-I42.9</td>
<td>Cardiomyopathy code range</td>
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<tr>
<td></td>
<td>I43</td>
<td>Cardiomyopathy in diseases classified elsewhere</td>
</tr>
<tr>
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<td>I50.1-I50.9</td>
<td>Heart failure code range</td>
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<tr>
<td></td>
<td>J41.0-J42</td>
<td>Chronic bronchitis code range</td>
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<tr>
<td></td>
<td>J44.0-J44.9</td>
<td>Other chronic obstructive pulmonary disease code range</td>
</tr>
<tr>
<td></td>
<td>P07.00-P07.32</td>
<td>Disorders of newborn related to short gestation and low birth weight, not elsewhere classified code range</td>
</tr>
<tr>
<td></td>
<td>P27.0-P27.9</td>
<td>Chronic respiratory disease originating in the perinatal period (includes bronchopulmonary dysplasia P27.1)</td>
</tr>
<tr>
<td></td>
<td>P28.0-P28.9</td>
<td>Other respiratory conditions originating in the perinatal period code range</td>
</tr>
<tr>
<td></td>
<td>Q20.0-Q28.9</td>
<td>Congenital malformations of the circulatory system code range</td>
</tr>
<tr>
<td></td>
<td>Z29.11</td>
<td>Encounter for prophylactic immunotherapy for respiratory syncytial virus (RSV)</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td>3E0234Z</td>
<td>Administration, physiological systems and anatomical regions, introduction, muscle, percutaneous, serum, toxoid and vaccine</td>
</tr>
<tr>
<td></td>
<td>3E0334Z</td>
<td>Administration, physiological systems and anatomical regions, introduction, peripheral vein, percutaneous, serum, toxoid and vaccine</td>
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</tbody>
</table>

**Type of service**

- Prescription drug

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Original Review Date: March 1999
### POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>02/13/14</td>
<td>Replace policy</td>
<td>Removed contradictory statement in the Rationale section about RSV-IVIg being contraindicated in children with cyanotic CHD.</td>
</tr>
<tr>
<td>09/11/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 7, 2014; references 1-2, 16-17, 20-22, 25, 27-28, 30, and 32 added; reference 31 updated.</td>
</tr>
<tr>
<td>10/15/15</td>
<td>Replace policy</td>
<td>Policy updated with literature review through September 8, 2015; references 2, 7, 10, and 33-34 added. Policy statements unchanged with the exception that prophylaxis in children over 2 years was added to the investigational statement.</td>
</tr>
<tr>
<td>08/11/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 10, 2016; references 2-4, 16-18, 26, and 31 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>08/30/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes to policy as noted. Policy updated with literature review through June 22, 2017; references 2, 9, 16, 19, and 22-24 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>08/20/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through June 4, 2018; no references added. Policy statements amended to clarify RSV prophylaxis and children with Down syndrome. For children with Down syndrome without other risk factors, RSV prophylaxis is considered investigational. Therefore, the clause “without other risk factors” was added to the policy statement. For children with Down syndrome and significant heart disease, RSV prophylaxis is considered medically necessary and is covered under section 1.c. in the policy statement.</td>
</tr>
</tbody>
</table>